AMENDMENTS TO THE DRAWINGS

Please replace original Figures 1, 2, 3, 4, 5, 6, and 7 with the Replacement Figures 1-1, 1-2, 2, 3, 4, 5, 6; 7-1, and 7-2 submitted concurrently herewith.

REMARKS

AMENDMENTS TO THE DRAWINGS

Figure 1 was amended to divide it into two sub-figures, Figure 1-1 and Figure 1-2, with the graphical depiction being divided into two separate halves with one half being resident in Figure 1-1 and the other half being resident in Figure 1-2 and labeled accordingly. Figure 1 was further amended to replace the text identifiers of each gene appearing to the right of the graphical depiction with each polynucleotides corresponding numerical identifier as listed in Table 2. The order of each polynucleotide presented in Figure 1 is identical to the order of each polynucleotide presented in Table 2. Figure 1 was further amended to substitute the cell line text identifiers appearing above each column of the graphical depiction with clear text identifiers. Each of these amendments were made to increase the clarity of the figure, and in particular, the polynucleotide and cell line text identifiers, in order to overcome the Examiner's objection to the same. No new matter has been added.

Figure 2 was amended to move the vertical dividing line between the "A" and "B" sides of each graph to their proper locations in accordance with the legend of Figure 2 on page 12. Figure 2 was further amended to substitute the numerical identifier at the top center of the Figure to take into account the division of Figure 7 into two separate halves as well as the division of Figure 1 into Figure 1-1 and Figure 1-2. No new matter has been added.

Figures 3 to 6 were amended to substitute the numerical identifier at the top center of each Figure to take into account the division of Figure 7 into two separate halves as well as the division of Figure 1 into Figure 1-1 and Figure 1-2. No new matter has been added.

Figure 7 was amended to divide it into two sub-figures, Figure 7-1 and Figure 7-2, with the graphical depiction being divided into two separate halves with one half being resident in Figure 7-1 and the other half being resident in Figure 7-2 and labeled accordingly. Figure 7 was further amended to delete the name of each of the 134 breast cancer cell lines tested as well as the series of hierarchical schemes resident between the Figure title and the graphical depiction. Both of the latter are not necessary for understanding the results conveyed since the "Potential Responders" are already adequately identified by the arrow above the depiction. Figure 7 was further amended to append numerical identifiers of each of the 137 polynucleotides represented along the Y-axis which is identical to the order of each polynucleotide presented in Table 2. Each of these amendments were made to increase the clarity of this figure, and in particular, the polynucleotide text identifiers, in order to overcome the Examiner's objection to the same.

Applicants note that since the amendments to the Figures merely represented "changes in reference characters, designations of figures...", Annotated Sheets have not been provided in accordance with MPEP 608.02(v).

AMENDMENTS TO THE SPECIFICATION

The Title of the specification was amended to substitute the phrase "IDENTIFICATION OF POLYNUCLEOTIDES" with the phrase "METHODS OF USING EphA2". These amendments were made solely to make the Title consonant with the claimed invention. No new matter has been added.

The Abstract beginning on page 131, line 2 was amended to delete the phrase ", through a weighted voting cross validation program,"; to delete the phrase "The expression level or phosphorylation status of some polynucleotides is regulated by treatment with a particular protein tyrosine kinase inhibitor compound, thus indicating that these polynucleotides are involved in the protein tyrosine kinase signal transduction pathway, e.g., Src tyrosine kinase."; to delete the phrase ", whose expression levels correlate highly with drug sensitivity or resistance and which are modulated by treatment with the compounds,"; and to delete the phrase "protein tyrosine kinase pathway, such as the Src tyrosine kinase pathway,". The Abstract was further amended to append the phrase "one or more of" immediately after the phrase "in which signaling through" and to append the phrase "aforementioned Src tyrosine and protein tyrosine kinases" after the "the" term residing after the added "one or more of" phrase. These amendments were made solely to overcome the Examiner's objection to the word length of the Abstract. The current Abstract contains 149 words. No new matter has been added.

STATUS OF THE CLAIMS:

Claims 1 to 40 and 52 are cancelled.

Claim 41 has been amended.

Claims 42 to 51 are withdrawn.

Claim 41 is pending.

Claim 41 was amended to delete the "Unigene Cluster No. Hs.171596 " phrase as well as to delete both the left and right parentheses on either side of the "EphA2" term; and amended to append the phrase "in a sample" after the "at least one informative gene" phrase. These amendments were made to overcome the Examiner's rejections and to place this claim in better condition for allowance. Applicants right to equivalents of Claim 41 is reserved. No new matter has been added.

Claim 41 was further amended to append the phrase ", and wherein said protein tyrosine kinase inhibitor is an inhibitor of one or more of the following: Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, EphA1, and EphA2", and to delete the "and" term prior to the second "wherein" term as a consequence of the prior amendment. Support for this amendment may be found on, e.g., pages 3 and 4 of the specification. Applicants assert that these amendments were not made to overcome any issues related to the patentability of this claim and that Applicants right to equivalents of Claim 41 is reserved. No new matter has been added.

I. Miscellaneous

a. Withdrawal of Claims 42 to 51

The Examiner has withdrawn Claims 42 to 51 stating

> ...Claims 42-51 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim...

Applicants believe the Examiner's withdrawal of Claims 42 to 51 was improper on account of Claim 41 not representing a generic claim in addition to Claims 42 to 51 not representing species claims of a genus. Specifically, Claim 41 refers to the measurement of "at least one informative gene" and lists that gene as being "EphA2". Claims 42 to 51 add **additional** elements to Claim 41 as evidenced by the use of the phrase "at least one additional gene" in each instance with each claim listing different genes that may be selected as representing "at least one additional gene". Since Claims 42 to 51 add additional elements to Claim 41, Claim 41 does not represent a genus since its scope does not encompass all of the limitations of Claims 42 to 51. In addition, Applicants also point out that since each of Claims 42 to 51 contain all of the limitations of its dependent Claim 41 (e.g., use of EphA2 as an informative gene for predicting resistance/sensitivity), examining these claims would not pose an undue burden on the Examiner since the allowability of these claims would depend upon the allowability of Claim 41 (e.g., the search of Claim 41 would be co-extensive with Claims 42 to 51 and no additional search would be required). Accordingly, Applicants request that the Examiner reconsider the withdrawal of Claims 42 to 51 and examine the same on the merits.

In addition, Applicants point out that withdrawal of Claims 42 to 51 is improper on account of the claims containing overlapping subject matter and thus not being mutually exclusive. According to the MPEP

> Where two or more species are claimed, ***a requirement for restriction to a single species may be proper if the species are mutually exclusive.*** < Claims ** to different species **>are mutually exclusive if< one claim recites limitations **>disclosed for< a first species but not * a second, while a second claim recites limitations disclosed only for the second species and not the first. This **>may also be< expressed by saying saying that >***to require restriction between claims limited to species, the< claims ** must not overlap in scope***<. (emphasis added)

(MPEP 806.04(f). Accordingly, Applicants request that the Examiner reconsider the withdrawal of Claims 42 to 51.

Nonetheless, if the Examiner maintains the withdrawal of Claims 42 to 51 on the basis that Claim 41 is a generic claim, Applicants remind the Examiner that upon the allowance of a generic claim, species claims depending from the genus claim should also be allowed. Specifically, the MPEP states

> Once a **>generic claim is allowable<, all of the claims drawn to species in addition to the elected species which *>require< all the limitations of the generic claim will ordinarily be * allowable >over the prior art< in view of the *>allowability< of the generic claim, since the additional species will depend thereon or otherwise *>require< all of the limitations thereof.

(MPEP 804.6(d)). Applicants believe Claim 41 is allowable and request that the withdrawal of Claims 42 to 51 be withdrawn on the ground that they are dependent upon an allowable independent claim and that Claims 42 to 51 be allowed accordingly.

b. <u>Objections to the Specification</u>

The Examiner has objected to the specification stating

> It is suggested the title be amended to reflect the instant invention, which is using the gene for EphA2 as a predictor for responsiveness of cancer cells to a kinase inhibitor.

In response, Applicants have amended the title to substitute the phrase "IDENTIFICATION OF POLYNUCLEOTIDES" with the phrase "METHODS OF USING EphA2".

The Examiner has objected to the specification stating

> The abstract is objected to for being too long.
>
> MPEP 608.0 l(b) states
>
> > The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

In response, Applicants have amended the Abstract to conform to the 150 word length limitation and point out that, on account of the amendments, the Abstract is now 149 words in length.

Applicants believe all of the Examiner's objections to the specification have been overcome in consideration of these amendments.

c. Objections to the Claims

The Examiner has objected to the Claims stating

> Claim 52 is objected to for reciting non-elected subject matter and being dependent upon non-elected claims.

In response, Applicants have cancelled Claim 52.

Applicants believe the Examiner's objection to the claims has been overcome in consideration of this amendment.

d. Objections to the Drawings

The Examiner has objected to the drawings stating

> Figures 1 and 7 are objected to because the Office's copies are illegible.
> Figure 2 is objected to for being confusing. The A panel of said figure does not have the same number of control and BMS-A treated samples; likewise, the B panel of said figure does not have the same number of control and BMS-A treated samples. The Examiner questions whether the vertical line separating panels A and B should be moved to the right.

In response, Applicants have submitted Replacement Figures 1-1, 1-2, 2, 3, 4, 5, 6, 7-1, and 7-2 which address and overcome the Examiner's objections to the drawings.

II. Rejections under 35 U.S.C. § 101

a. The Examiner has rejected 41 and 52 under 35 U.S.C. § 101, alleging that the claimed invention is unpatentable over Claims 1-14 of US Application 10/648,593 under the judicially created obviousness-type double patenting doctrine. More particularly, the Examiner alleges:

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *ht re Berg,* 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Ch'. 1998); ht re *Goodman,* 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Claims 41 and 52 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 16 of US Application 11/072,175. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 41 and 52 herein and Claim 16 of 11/072,175 me both directed to methods for determining the effect of a compound on the expression of gene products. Specifically, they are directed to determining the effect of BMS-A on the expression of gene products from the Hs. 171596 (EphA2) gene. The claims differ in that Claim 16 of 11/072,175 also recites methods for determining the effect of additional compounds on the expression of additional gene products. The portion of the specification in 11/072,175 (Table 2; Fig 4) that supports the recited methods includes embodiments that would anticipate Claims 41 and 52 herein, e.g., methods for determining the effect of BMS-A on the expression of gene products from the Hs. 171596 (EphA2) gene. Claims 41 and 52 herein cannot be considered patentably distinct over Claim 16 of 11/072,175 when there are specifically recited embodiments, methods for determining the effect of BMS-A on the expression of gene products from the Hs. 171596 (EphA2) gene, that would anticipate Claims 41 and 52 herein. Alternatively, Claims 41 and 52 herein cannot be considered patentably distinct over Claim 16 of 11/072,175 when there are specifically disclosed embodiments in 11/072,175 that supports Claim 16 of that application and falls within the scope of Claims 41 and 52 herein, because it would have been obvious to a skilled artisan to modify the methods of Claim 16 of 11/072,175 by selecting a specifically disclosed embodiment that supports those claims, i.e., methods for determining the effect of BMS-A on the expression of gene products from the Hs. 171596 (EphA2) gene, as disclosed in 11/072,175. One having ordinary skill in the art would have been motivated to do this, because such an embodiment is disclosed as being a preferred embodiment within Claim 16 of 11/072,175.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants respectfully disagree with the Examiners allegation that Claims 41 and 52 of the instant specification and Claim 16 of U.S. Serial No. 11/072,175 are "not patentably distinct". However, Applicants note that the Examiner's rejection is "provisional" and in accordance with MPEP 804(I)(B), no action is required on behalf of Applicants.

Applicants also point out that, in accordance with MPEP 804(I)(C), when two applications are filed by the same inventive entity or by different inventive entities having a common inventor, and/or common assignee, that "if the 'provisional' double patenting rejection in one application is the only rejection remaining in that application, the examiner should then

withdraw that rejection and permit the application to issue as a patent, thereby converting the 'provisional' double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent." Since Applicants believe all of the Examiners rejections have been overcome in consideration of Applicants amendments and/or arguments presented herein, Applicants respectfully request the instant application be allowed to issue and that the obviousness-type double patenting rejection of Claim 41 under 35 U.S.C. § 101 be withdrawn. However, in the sole interest of facilitating prosecution, Applicants have cancelled Claim 52. Accordingly, the rejection of Claim 52 under 35 U.S.C. § 101 has been rendered moot.

III. Rejections under 35 U.S.C. § 112, Second Paragraph

a. The Examiner has rejected Claims 41 and 52 under 35 U.S.C. § 112, second paragraph, alleging that these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More particularly, the Examiner alleges

> Claim 41 recites the gene for EphA2 by a database accession number, Hs. 171596, which is accessed by the internet. USPTO policy does not permit the USPTO, i.e, via an issued patent, to link to any commercial sites, since the USPTO exercises no control over the organization, views, or accuracy of the information contained on these outside sites and the content within is likely to change over time. In addition, the sequence found at said site, set forth by GenBank Accession Number NM_004431 as disclosed in Table 2, is not identical to SEQ ID NO: 1 herein (see enclosed alignment). Claim 53, as dependent from Claim 41, is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the same reason.
>
> Claim 41 recites the limitation "said sample" in lines 5 and 6. There is insufficient antecedent basis for this limitation in the claim. Claim 53, as dependent from Claim 41, is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the same reason.

In response and in specific relation to the use of the Unigene Cluster Accession in Claim 41, Applicants have amended Claim 41 to delete the "Unigene Cluster No. Hs.171596 " phrase as well as to delete both the left and right parentheses on either side of the "EphA2" term.

Regarding the sequence disparity between the sequence provided at Genbank Accession gi|NM_004431 and the sequence provided as SEQ ID NO:1, Applicants point out to the Examiner that the Unigene Cluster sequence represents the combined consensus of all known

EphA2 sequences and thus would not be expected to exactly match the sequence provided as SEQ ID NO:1.

Regarding the "said sample" limitation, Applicants have amended Claim 41 to append the phrase "in a sample" after the "at least one informative gene" phrase.

Applicants believe the Examiner's rejection of Claim 41 under 35 U.S.C. § 112, second paragraph has been overcome in consideration of these amendments. In addition, the Examiner's rejection of Claim 52 has been rendered moot in consideration of Applicants cancellation of the same.

IV. Rejections under 35 U.S.C. § 112, First Paragraph

a. The Examiner has rejected Claims 41 and 52 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same. More particularly, the Examiner alleges

> Claims 42 and 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for methods of identifying breast cancer cells that are sensitive to BMS-A or any tyrosine kinase inhibitor by determining the effect of any said tyrosine kinase inhibitor on the expression of any EphA2 gene product in any breast cancer cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.
>
> In regards to this enablement rejection, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the m~; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the m-t. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.
>
> Claim 42 is so broad as to encompass a method of identifying breast cancer cells that are resistant or sensitive to treatment with any protein tyrosine kinase inhibitor by determining the effect of any said protein tyrosine kinase inhibitor on the expression of an EphA2 gene product in any said breast cancer cells. Claim 52 is so broad as to encompass a method of identifying breast cancel' cells that me resistant or sensitive to treatment with the BMS-A protein tyrosine kinase inhibitor by

determining the effect of BMS-A on the expression of art EphA2 gene product in any said breast cancer cells. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the large number of protein tyrosine kinase inhibitors and large number of breast cancer cells broadly encompassed by the claim.

The specific reagents and steps used for identifying any breast cancer cell that can be successfully treated with any protein tyrosine kinase inhibitor determine the method's success. Predictability of which steps and reagents can be used to obtain the desired effect requires a knowledge of how said steps and reagents relate to the desired outcome. Specifically, predictability of which of the large number of breast cancer cells can be contacted with any one of a large number protein tyrosine kinase inhibitors in order to deter-mine which breast cancer cells can be successfully treated with any one of said inhibitors requires guidance with regard to which each breast cancel" cells have a protein tyrosine kinase that is inhibited by any specific inhibitor, whether inhibition of said tyrosine kinase regulates the expression of an EphA2 gene product, and whether inhibition of said EphA2 gene product would have the desired effect of treating the breast cancer cell. However, in this case the disclosure is limited to a method of using "BMS-A" kinase inhibitor for correlating regulation of an EphA2 gene expression product with treatment of breast cancer cells; however, the structure of the "BMS-A" kinase inhibitor is [sic] not disclosed by the specification or the art.

Methods for testing the effects of any compound on the activity of any protein tyrosine kinase as well as methods for testing the effect of any compound on expression of an EphA2 gene product and on the ability to inhibit the growth of breast cancer cells are known in the However, it is not routine in the art to screen an essentially unlimited number of compounds as protein tyrosine kinase inhibitors or to screen a ve~3' large number of compounds that me known protein tyrosine kinase inhibitors for an effect on EphA2 gene expression and on the growth of a large number of breast cancer cells. Furthermore, the steps and reagents to be used with a reasonable expectation of success in obtaining the desired treatment of identifying breast cancer cells that can be successfully treated are limited and unpredictable (Fernandez-Trigo et al, 1995; Woll, et al 1999). In addition, one skilled in the art would expect any tolerance to modification of any successful method for identifying breast cancer cells that can be successfully treated with a protein tyrosine kinase inhibitor to diminish with each further and additional modification of steps and reagents used.

The specification does not support the broad scope of Claim 42 which, encompasses all methods of identifying breast cancer cells that are resistant or sensitive to treatment with any protein tyrosine kinase inhibitor by determining the effect of any said protein tyrosine kinase inhibitor on the expression of an EphA2 gene product in any said breast cancer cells. The specification also does not support the broad scope of Claim 53, which encompasses all methods of identifying breast cancer cells that are resistant or sensitive to treatment with the BMS-A protein tyrosine kinase inhibitor by determining the effect of BMS-A on the expression of an EphA2 gene product in any said breast cancer cells. The specification does not support the broad scope of Claims 42 and 52 because the specification does not establish: (A) the structure of any protein tyrosine kinase inhibitor, including BMS-A, that can be used to identify breast cancer cells that can be successfully treated with

the inhibitor by determining the effect of the inhibitor on the expression of an EphA2 gene product; (B) regions of the inhibitor structure which may be modified without effecting the kinase inhibition and treatment of breast cancer cells; (C) the general tolerance of the kinase inhibition and treatment of breast cancer cells to modification of the inhibitor structure and extent of such tolerance; (D) a rational and predictable scheme for modifying any protein tyrosine inhibitor with an expectation of obtaining the desired biological function; (E) the types of breast cancer cells that comprise any specific protein tyrosine kinase that is inhibited by any specific kinase inhibitor and whether inhibition of said kinase inhibits growth of the breast cancer cell; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices compounds are protein tyrosine kinase inhibitors and which breast cancer cells would be successfully inhibited by said kinase inhibitors.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method for identifying any number of breast cancer cells that are sensitive to "BMS-A" or any tyrosine kinase inhibitor by determining the effect of any said tyrosine kinase inhibitor on the expression of any EphA2 gene product in any said breast cancer cell. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants disagree with the Examiner's allegations and assert that the specification as originally filed would in fact enable one skilled in the art to make and use the invention encompassed by Claims 41 and 52. First, Applicants assert that the invention encompassed by Claim 41 is not "unpredictable" as alleged by the Examiner, but rather has been demonstrated to work for its intended purpose of predicting which breast cancer cells are likely to be resistant or sensitive to a protein tyrosine kinase inhibitor. Specifically, the instant specification demonstrates that 137 predictor polynucleotides listed in Table 2 of the instant application, which includes the EphA2 receptor, caveolin 1, and caveolin 2 polynucleotides, in addition to the 40, 15, and 7 predictor polynucleotide sets listed in Tables 2, 4, and 5 of the instant application, respectively, can predict the sensitivity and resistance of breast cancer cells with reasonable accuracy to a compound inhibitor of members of the Src family of tyrosine kinases, including e.g., Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, PDGFR, c-kit and Eph receptors. The prediction accuracy of the 137, 40, 15, and 7 predictor polynucleotide sets are shown in Figures 5 and 6. The EphA2 receptor, caveolin 1, and caveolin 2 polynucleotides are part of the 137 and 40 predictor sets. In addition, EphA2

receptor, caveolin 1, and caveolin 2 polynucleotides were determined to be specifically modulated by BMS-A as shown in Table 2 (see column entitled "Modulated by BMS-A") as well as in Figure 3. Furthermore, in addition to demonstrating that the invention works for its intended purpose, the specification also provides requisite teachings in Examples 1 and 2, pages 30 to 42, and in Tables 1 to 6, which would enable one skilled in the art to make and use the invention.

Applicants assert that based upon the teachings of the specification, and in particular, the provision of experimental results demonstrating that the 137, 40, 15, and 7 predictor gene sets, including the EphA2 receptor, caveolin 1, and caveolin 2 polynucleotides, are able to predict the sensitivity and resistance of breast cancer cells with reasonable accuracy, in conjunction with the explicit teachings of how to peform the experiments, one skilled in the art could readily make and use the invention.

Although Applicants believe the specification, as originally filed, adequately enables one skilled in the art to make and use the claimed invention, Applicants provide additional evidence to support its assertions. Applicants bring to the attention of the Examiner a 37 C.F.R. § 1.131 Declaration (referred to herein as the "Huang Declaration") and its accompanying Exhibits A, B, C, D, E, F, G, H, I, J, K, and L (submitted concurrently herewith). The Huang Declaration demonstrates that the 137 predictor polynucleotides listed in Table 2 of the instant application, including the EphA2 receptor, caveolin 1, and caveolin 2 polynucleotides, in addition to the 40, 15, and 7 predictor polynucleotide sets listed in Tables 2, 4, and 5 of the instant application, respectively, can predict the sensitivity and resistance of breast cancer cells with reasonable accuracy to not only BMS-A, but also several other compound inhibitors of members of the Src family of tyrosine kinases, including e.g., Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, PDGFR, c-kit and Eph receptors (e.g., BMS-B, BMS-C, BMS-D, and BMS-E), with an accuracy ranging between 74% to 96%. The same methods taught by the instant specification were used to perform the experiments in the Huang Declaration. As stated in the Huang Declaration,

> These results unequivocally establish the utility of these predictor polynucleotides, in the identification of breast cancer cells that are resistant or sensitive to Src tyrosine kinase / Bcr-abl, PDGFR, c-kit and Eph protein tyrosine kinase inhibitors as demonstrated using a representative number of five such inhibitors. The results also unequivocally establish the utility of using the EphA2

> receptor, caveolin 1, and/or caveolin 2 polynucleotides as predictors, either alone or in combination.
>
> Accordingly, the utility of these predictor polynucleotide sets, in addition to the EphA2 receptor, caveolin 1, and/or caveolin 2 polynucleotides, is not solely limited to predicting the resistance or sensitivity of breast cancer cells to BMS-A, but rather to any Src tyrosine kinase / Bcr-abl, PDGFR, c-kit and Eph protein tyrosine kinase inhibitor as demonstrated herein using a representative number of five such inhibitors.

(see section 4 of the Huang Declaration).

The Huang Declaration also demonstrates that the EphA2 receptor, either alone or in conjunction with either caveolin 1 or caveolin 2, can predict the sensitivity and resistance of breast cancer cells to several inhibitors of members of the Src family of tyrosine kinases / Bcr-abl, PDGFR, c-kit and Eph protein tyrosine kinases, including BMS-A, BMS-B, BMS-C, BMS-D, and BMS-E, with an accuracy ranging between 78% to 91% for EphA2 alone, between 61% to 74% for the combination of EphA2 and caveolin-1, and between 65% to 74% for the combination of EphA2 and caveolin-2 for each of the compounds. The Huang Declaration states

> ...The results compare favorably to the 7, 15, 40, and 137 predictor polynucleotide set predictions described herein. These results unequivocally establish the utility of the EphA2 receptor polynucleotide, either alone or in combination with either caveolin 1 or caveolin 2 polynucleotides, in the identification of breast cancer cells that are resistant or sensitive to Src tyrosine kinase / Bcr-abl, PDGFR, c-kit and Eph protein tyrosine kinase inhibitors as demonstrated using a representative number of five such inhibitors.
>
> Accordingly, the utility of the EphA2 receptor, either alone or in combination with either caveolin 1 or caveolin 2 polynucleotides is not solely limited to predicting the resistance or sensitivity of breast cancer cells to BMS-A, but rather to any Src tyrosine kinase / Bcr-abl, PDGFR, c-kit and Eph protein tyrosine kinase inhibitor as demonstrated herein using a representative number of such inhibitors.

(see section 6 of the Huang Declaration).

Accordingly, Applicants assert one skilled in the art could make and use the invention encompassed by Claim 41 based upon the teachings provided in the specification as originally filed, as supported by the corroborative teachings of the Huang Declaration submitted herewith.

Applicants disagree with the Examiner's implication that the structure of BMS-A is required to enable the claimed invention. Specifically, Applicants point out the Examiner that Claim 41 is broadly directed to protein tyrosine kinase inhibitors and is thus not specific to BMS-A. While BMS-A was used to identify the predictor polynucleotide sets that served as a basis for the claimed method, the method is not specific to predicting the sensitivity or resistance to only

BMS-A, but rather to any other protein tyrosine kinase inhibitor. The specification states

> The present invention describes the identification of marker polynucleotides whose expression levels are highly correlated with drug sensitivity in breast cell lines that are either sensitive or resistant to protein tyrosine kinase inhibitor compounds. More particularly, the protein tyrosine kinases that are inhibited in accordance with the present invention include members of the Src family of tyrosine kinases, for example, Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, Jak, PDGFR, c-kit and Eph receptors.

(see first paragraph of Summary of the Invention on p.3). The latter is directly supported by the corroborative teachings of the Huang Declaration since it demonstrated the claimed methods ability to predict the sensitive / resistant classification accuracy of breast cancer cell lines using a representative number of four additional protein tyrosine kinase inhibitors. Clearly, disclosing the structure of BMS-A is not required for the skilled artisan to make and use the invention since neither the claims nor the specification limit the invention to predicting breast cancer cells that are sensitive / resistant to BMS-A. Rather, the claim method is meant predict the sensitivity or resistance of breast cancer cells to be used with any protein tyrosine kinase inhibitor, in general. Applicants point out that while the Huang Declaration does disclose the structures of BMS-A, -B, -C, -D, and –E in Exhibit L, the latter was solely provided to demonstrate to the Examiner that each of these compounds were disclosed in the WO 00/62778 application.

However, in the sole interest of facilitating prosecution, Applicants have amended Claim 41 to append the phrase "and wherein said protein tyrosine kinase inhibitor is an inhibitor of one or more of the following: Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, EphA1, and EphA2." Applicants believe the Examiner's rejection of Claim 41 under 35 U.S.C. § 112, first paragraph has been overcome in consideration of this amendment and respectfully request that it be withdrawn. In addition, Applicants have rendered the Examiner's rejection of Claim 52 under 35 U.S.C. § 112, first paragraph moot as a consequence of the cancellation of the same.

Applicants also disagree with the Examiner's allegation that Claim 41 is not enabling for failure to provide the following:

> (A) the structure of any protein tyrosine kinase inhibitor, including BMS-A, that can be used to identify breast cancer cells that can be successfully treated with the inhibitor by determining the effect of the inhibitor on the expression of an EphA2 gene product; (B) regions of the inhibitor structure which may be modified without

effecting the kinase inhibition and treatment of breast cancer cells; (C) the general tolerance of the kinase inhibition and treatment of breast cancer cells to modification of the inhibitor structure and extent of such tolerance; (D) a rational and predictable scheme for modifying any protein tyrosine inhibitor with an expectation of obtaining the desired biological function; (E) the types of breast cancer cells that comprise any specific protein tyrosine kinase that is inhibited by any specific kinase inhibitor and whether inhibition of said kinase inhibits growth of the breast cancer cell; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices compounds are protein tyrosine kinase inhibitors and which breast cancer cells would be successfully inhibited by said kinase inhibitors.

Re: sub-part (A), Applicants addressed this *supra* and argued the structure of BMS-A is not required to enable the claimed invention since Claim 41 as originally presented is directed to a method of determining whether breast cancer cells are sensitive or resistant to protein tyrosine kinase inhibitors, in general, and is not specific to any one protein tyrosine kinase inhibitor, such as BMS-A Moreover, Claim 41 as currently amended, is directed to a method of determining whether breast cancer cells are sensitive or resistant to protein tyrosine kinase inhibitors, wherein said "protein tyrosine kinase inhibitor is an inhibitor of one or more of the following: Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, EphA1, and EphA2", and the Huang Declaration submitted concurrently herewith establishes that the method can predict whether breast cancer cells are resistant or sensitive to a representative number of four additional protein tyrosine kinase inhibitors that are also inhibitors of Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, EphA1, and EphA2 (see Lombardo et al., J. Med. Chem., 47:6658-6661 (2004); and the Huang Declaration submitted herewith).

Re: sub-parts (B), (C), and (D), Applicants assert the Examiner's rationale for rejecting Claims 41 and 52 under 35 U.S.C. § 112, first paragraph on the grounds conveyed in these sub-parts is in error. First, Applicants point out that Claim 41 is directed to methods of predicting whether breast cancer cells will be sensitive or resistant to a protein tyrosine kinase inhibitor, and is not directed to composition of matter claims directed to a genus of protein tyrosine kinase inhibitors. As a consequence, the proper question is whether the instant specification provides sufficient teachings to enable one skilled in the art to make and use the claimed invention, not whether the specification teaches the structure of protein tyrosine kinase inhibitors and not whether the specification teaches how such inhibitors can be modified. As discussed *supra*, the instant specification does provide such requisite teachings, in addition to demonstrating that the predictor polynucleotides can accurately predict whether breast cancer cells are sensitive or resistant to a protein tyrosine kinase inhibitor regardless of its structure. In addition, the Huang

Declaration provides additional support that the claimed invention, as described and enabled by the specification as originally filed, is able to predict which breast cancer cell lines are sensitive and resistant to other protein tyrosine kinase inhibitors.

Re: subpart (E), Applicants disagree with the Examiner's allegation that a skilled artisan would require a specific teaching of the type of breast cancer cells that have a protein tyrosine kinase that can be inhibited. Specifically, the nature of the invention is such that if a particular breast cancer cell does not express a protein tyrosine kinase that can be inhibited by a protein tyrosine kinase inhibiter, the breast cancer cell would simply be classified as being resistant. A skilled artisan would not require explicit teachings of which breast cancer cells should be used with the invention since the invention is designed to predict which breast cancer cells are resistant or sensitive to a protein tyrosine kinase inhibitor. As a consequence, it would be improper to require the specification to teach what the method is designed to address – namely which breast cancer cells are breast cancer cells that are resistant or sensitive to a protein tyrosine kinase inhibitor. To require the specification to provide such teachings would be akin to requiring patent applications directed to methods of screening for inhibitors of protein X, for example, to contain detailed descriptions of every conceivable inhibitor that could be identified by the method. Such a requirement would be onerous, if not impossible, and clearly inconsistent with the requirements under 35 U.S.C. § 112, first paragraph, which merely requires a specification to teach how one skilled in the art could make and use the invention which the instant specification adequately satisfies. A patent specification is not intended nor required to be a production specification. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1536, 3 USPQ2d 1737, 1745 (Fed. Cir. 1987); *In re Gay*, 309 F.2d 768, 135 USPQ 311 (CCPA 1962).

In addition, Applicants point out that a skilled artisan would not require identification of which types of breast cancer cells that could be used with the invention since the art recognizes the members of the protein tyrosine kinase family, including c-Src, play "a major role in the development, growth, progression, and metastasis of a wide variety of human cancers" and that "Src activation, in the form of elevated kinase activity and/or protein expression levels, has been demonstrated in several major cancer types, including...breast...carcinomas" (see p. 6658 of Lombardo et al., J. Med. Chem., 47:6658-6661 (2004); and Frame et al., Biochim. Biophys. Acta, 1602:114-130 (2002)). It is also known that other protein tyrosine kinases are also implicated in the incidence of breast cancer as well (see Hynes, Breast Cancer Res., 2:154-157 (2000); submitted concurrently herewith). Clearly, descriptions of which breast cancer cell lines

can be used in the claimed method are not necessary since the skilled artisan would already appreciate that protein tyrosine kinases play a major role in the incidence of breast cancer and would be expected to express a protein tyrosine kinase that could be inhibited by a protein tyrosine kinase inhibitor.

Furthermore, Applicants point out that the specification already provides descriptions of 23 breast cancer cell lines, which are a representative sample of the various types of breast cancer cells, in addition to providing experimental results that establish the ability of the claimed method to predict which of the tested breast cancer cells are resistant or sensitive to a protein tyrosine kinase inhibitor, in addition to teaching the resistant or sensitive results of 134 breast cancer tissue samples (see Figure 7). Clearly, a skilled artisan would be able to make and use the invention based upon the teachings of the instant specification as originally filed.

However, as noted *supra*, in the sole interest of facilitating prosecution, Applicants have amended Claim 41 to append the phrase "and wherein said protein tyrosine kinase inhibitor is an inhibitor of one or more of the following: Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, EphA1, and EphA2." Applicants believe the Examiner's rejection of Claim 41 under 35 U.S.C. § 112, first paragraph has been overcome in consideration of this amendment and respectfully request that it be withdrawn. In addition, Applicants have rendered the Examiner's rejection of Claim 52 under 35 U.S.C. § 112, first paragraph moot as a consequence of the cancellation of the same.

Applicants disagree with the Examiner's application of Fernandez-Trigo et al. and Woll et al., to support her reasonable expectation of success argument. First, Applicants point out that neither Woll et al., nor Fernandez-Trigo et al. are relevant for breast cancer nor to protein tyrosine kinase inhibitors. Rather, Woll et al. is solely applicable to metastatic disease in uveal melanoma, while Fernandez-Trigo et al. is solely applicable to sensitivity assays for colorectal and appendiceal cancer – indications that are subject to different pathways of incidence and thus mechanistically unrelated to breast cancer. Applicants also point that the Examiner has failed to establish any connection between these indications and breast cancer nor to protein tyrosine kinase inhibitors. Accordingly, the basis for the Examiner's limited and unpredictable steps rationale are not relevant to the claimed method designed to predict sensitivity / resistance of breast cancer to protein tyrosine kinase inhibitors. Secondly, the Examiner's argument appears to be premised on the unpredictability of in vitro predictions and their subsequent application to treatment regimens. Applicants assert the latter is irrelevant to the invention as currently claimed

since none of the claims are directed to in vivo methods of treatment. While the invention encompassed by Claim 41 could rationally be used as a basis for establishing treatment regimens for protein tyrosine kinase inhibitors, the Examiner's basis for this rejection is in error since the instant claims do not contain such a limitation.

V. Rejections under 35 U.S.C. § 112, First Paragraph

a. The Examiner has rejected Claims 41 and 52 under 35 U.S.C. § 112, first paragraph, alleging that these claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, has possession of the claimed invention. More particularly, the Examiner alleges

> These claims are directed to a genus of methods for identifying any number of breast cancer cells that are sensitive to "BMS-A" or any tyrosine kinase inhibitor by determining the effect of any said tyrosine kinase inhibitor on the expression of any EphA2 gene product in any said breast cancer cell. The specification teaches no representative species of such methods. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a method for identifying any number of breast cancer cells that are sensitive to "BMS-A" or any tyrosine kinase inhibitor by determining the effect of any said tyrosine kinase inhibitor on the expression of any EphA2 gene product in any said breast cancer cell. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.
>
> Examiner's note: R is acknowledged that the specification states: "The protein tyrosine kinase inhibitor compound, BMS-A, utilized for identifying the polynucleotide predictor sets of this invention, was described in WO 00/62778, published Oct. 26, 2000". However, searching a PDF version of WO 00/62778 for the terms "BMS-A" and "BMS" failed to reveal to the Examiner any information on a compound named "BMS-A'.

Applicants disagree with the Examiner's allegation and assert that the invention encompassed by Claims 41 and 52 is described in the specification in such a way that a skilled artisan would recognize that the inventors had possession of the claimed invention at the time the application was filed. First, Applicants disagree with the Examiner's characterization of the claimed method as "a genus of methods" requiring the teaching of a number of "representative

species" for the reasons outlined herein. The Examiner's basis appears to imply that the invention encompasses multiple breast cancer cells as well as multiple protein tyrosine kinase inhibitors to function and as a result a representative number of species for both breast cancer cells and protein tyrosine kinase inhibitors is required to establish Applicants were in possession of the invention. Applicants disagree with this basis and point out that her characterization is not representative of the claimed invention. The claimed invention is merely directed to a method of predicting whether a given breast cancer cell is resistant or sensitive to a protein tyrosine kinase inhibitor. As noted *supra*, a skilled artisan would not require detailed descriptions of which breast cancer cells can be used with the invention. Rather, it would be improper to require the specification to teach that which the method was designed to address – namely which breast cancer cells are resistant or sensitive to a protein tyrosine kinase inhibitor. In addition, since the invention is directed to predicting whether breast cancer cells are resistant or sensitive to any given protein tyrosine kinase inhibitor, it would also be improper to require that the specification teach the structure of all such inhibitors that could be tested.

In addition, the claimed method is in fact described in the specification as originally filed, and is not "unpredictable" as alleged by the Examiner, but rather has been demonstrated to work for its intended purpose of predicting which breast cancer cells are likely to be resistant or sensitive to a protein tyrosine kinase inhibitor. Specifically, the instant specification demonstrates that 137 predictor polynucleotides listed in Table 2 of the instant application, which includes the EphA2 receptor, caveolin 1, and caveolin 2 polynucleotides, in addition to the 40, 15, and 7 predictor polynucleotide sets listed in Tables 2, 4, and 5 of the instant application, respectively, can predict the sensitivity and resistance of breast cancer cells with reasonable accuracy to a compound inhibitor of members of the Src family of tyrosine kinases, including e.g., Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, PDGFR, c-kit and Eph receptors. The prediction accuracy of the 137, 40, 15, and 7 predictor polynucleotide sets are shown in Figures 5 and 6. The EphA2 receptor, caveolin 1, and caveolin 2 polynucleotides are part of the 137 and 40 predictor sets. In addition, EphA2 receptor, caveolin 1, and caveolin 2 polynucleotides were determined to be specifically modulated by BMS-A as shown in Table 2 (see column entitled "Modulated by BMS-A") as well as in Figure 3. Furthermore, in addition to demonstrating that the invention works for its intended purpose, the specification also provides requisite teachings in Examples 1 and 2, pages 30 to 42, and in Tables 1 to 6, which would enable one skilled in the art to make and use the

invention as well as to demonstrate that Applicants were in possession of the same.

However, and contrary to the Examiner's basis noted above, the invention does in fact teach the result of using the method to predict the sensitive / resistant classification of 23 different breast cancer cell lines to a protein tyrosine kinase inhibitor as well as providing the results of predicted resistant / sensitive classification results of 134 additional breast tumor samples (see Figure 7) which would clearly constitute a representative number. Nonetheless, Applicants point out that whether a representative number is demonstrated is irrelevant since the invention does not require the use of any of these breast cancer cell lines - rather these cell lines were only being used to demonstrate that the claimed invention works for its intended purpose.

In addition, Applicants also disagree with the Examiner that the structure of BMS-A, or even the structures of other protein tyrosine kinase inhibitors is necessary to establish Applicants were in possession of the claimed invention, as argued elsewhere herein.

Although Applicants believe the specification, as originally filed, provides adequate teachings to convince one skilled in the art that Applicants were in possession of the claimed invention, Applicants brought to the attention of the Examiner a 37 C.F.R. § 1.131 Declaration (referred to herein as the "Huang Declaration") and its accompanying Exhibits A, B, C, D, E, F, G, H, I, J, K, and L (submitted concurrently herewith) which demonstrated that the 137 predictor polynucleotides listed in Table 2 of the instant application, including the EphA2 receptor, caveolin 1, and caveolin 2 polynucleotides, in addition to the 40, 15, and 7 predictor polynucleotide sets listed in Tables 2, 4, and 5 of the instant application, respectively, can predict the sensitivity and resistance of breast cancer cells with reasonable accuracy to not only BMS-A, but also several other compound inhibitors of members of the Src family of tyrosine kinases, including e.g., Src, Fgr, Fyn, Yes, Blk, Hck, Lck and Lyn, as well as other protein tyrosine kinases, including, Bcr-abl, PDGFR, c-kit and Eph receptors (e.g., BMS-B, BMS-C, BMS-D, and BMS-E), with an accuracy ranging between 74% to 96%. The same methods taught by the instant specification were used to perform the experiments in the Huang Declaration.

The Huang Declaration, also demonstrated that the EphA2 receptor, either alone or conjunction with either caveolin 1 or caveolin 2, can predict the sensitivity and resistance of breast cancer cells to several inhibitors of members of the Src family of tyrosine kinases / Bcr-abl, PDGFR, c-kit and Eph protein tyrosine kinases, including BMS-A, BMS-B, BMS-C, BMS-D, and BMS-E, with an accuracy ranging between 78% to 91% for EphA2 alone, between 61%

to 74% for the combination of EphA2 and caveolin-1, and between 65% to 74% for the combination of EphA2 and caveolin-2 for each of the compounds.

However, as noted *supra*, in the sole interest of facilitating prosecution, Applicants have amended Claim 41 to append the phrase "and wherein said protein tyrosine kinase inhibitor is an inhibitor of one or more of the following: Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, EphA1, and EphA2." Applicants believe the Examiner's rejection of Claim 41 under 35 U.S.C. § 112, first paragraph has been overcome in consideration of this amendment and respectfully request that it be withdrawn. In addition, Applicants have rendered the Examiner's rejection of Claim 52 under 35 U.S.C. § 112, first paragraph moot as a consequence of the cancellation of the same.

V. Rejections under 35 U.S.C. § 103(a)

a. The Examiner has rejected Claim 41 under 35 U.S.C. § 103(a), as being unpatentable over Kassenbrock et al, 2002 in view of Wang et al, 2002 and further in view of Ogawa et al, 2000. More particularly, the Examiner alleges

> Kassenbrock et al teach that, in a human breast cancer cell line, the Src-class tyrosine kinase inhibitor PPI inhibits Cbl phosphorylation (Fig 6) and EGF-R ubiquitination (Fig 8) leading to the proposal that phosphorylation of Cbl by a Src-class kinase leads to ubiquitination and down-regulation of the EGF-R (pg 24974; parg 8). Kassenbrock et al do not teach that PP1 regulates the expression level of EphA2. Wang et al teach that Cbl down-regulates EphA2 (Fig 2). Based on said teachings, a person of ordinary skill in the art would believe that, more likely than not, PP1 by inhibiting Cbl phosphorylation would also down-regulate EphA2. Ogawa et al teach that EphA2 is highly expressed in breast cancer cells and that inhibition of EphA2 function inhibits tumor neovascularization (Fig 1; Table 1; Abstract). Thus, based on the combined teachings of Kassenbrock et al, Wang et al, and Ogawa et al, the skilled artisan would believe that, more likely than not, down-regulation of EphA2 by PP 1 would inhibit tumor growth and survival by inhibiting tumor neovascularization (see specifically Ogawa et al, pg 6044, parg 1). It would have been obvious to a person of ordinary skill in the art to use the method of Kassenbrock et al. to test the effect of PP1 on EphA2 expression levels in breast cancer cells and to conclude that, if EphA2 was down-regulated by PP1, the cancer cells would be sensitive to treatment with PP1. Motivation to use said methods derives from the desire to determine if PP 1 would be successful for treatment of a patient with breast cancer. The expectation of success is high, as high levels of EphA2 are predictive of tumor growth and the art teaches that, more likely than not, PPI, via inhibition of Cbl phosphorylation, would down-regulate EphA2. Therefore, Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kassenbrock et al, 2002 in view of Wang et al, 2002 and further in view of Ogawa et al, 2000.

Applicants disagree with the Examiner's allegation and assert that the invention encompassed by Claims 41 and 52 is not obvious over Kassenbrock et al, 2002 in view of Wang et al, 2002 and further in view of Ogawa et al, 2000 and assert that the Examiner's rejection of these claims under 35 U.S.C. § 103(a), is in error. First, Applicants remind the Examiner that before a rejection of a claim under 35 U.S.C. § 103(a) can properly be made, each of the following must be established

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must ***teach or suggest all the claim limitations***.(emphasis added)

(MPEP 2143). Neither Kassenbrock et al., Wang et al., nor Ogawa et al., alone or in combination, teach all of the limitations of Claim 41. Specifically, neither of these publications teache a method for predicting whether a breast cancer cell will be resistant or sensitive to a protein tyrosine kinase inhibitor by measuring the expression level of the EphA2 receptor. As a consequence, Applicants submit that the third prong of 35 U.S.C. § 103(a) is not satisfied since these publications fail to "teach or suggest all the claim limitations". In addition, the Examiner has failed to cite any other publication that could be used, either alone or in combination with Kassenbrock et al., Wang et al., or Ogawa et al., that teaches all of the limitations of Claim 41. If fact, the Examiner acknowledges that Kassenbrock et al. does "not teach that PP1 regulates the expression level of EphA2".

In addition, the Examiner's rejection of Claim 41 under 35 U.S.C. § 103(a) is also in error for failing to satisfy the second and third prongs of 35 U.S.C. § 103(a). Specifically, the Examiner hypothesizes that since Kassenbrock et al. teach that "phosphorylation of Cbl by a Src-class kinase leads to ubiquitination and down-regulation of the EGF-R" and since Wang et al. teaches that "Cbl down-regulates EphA2" and since Ogawa et al. teach that "EphA2 is highly expressed in breast cancer cells and that inhibition of EphA2 function inhibits tumor neovascularization", "one skilled artisan would believe that, more likely than not, down-regulation of EphA2 by PP 1 would inhibit tumor growth and survival by inhibiting tumor neovascularization". The Examiner's logic is in error and contrary to the teachings of the cited publications. First, while Kassenbrock et al. do teach that the PP1 Src-kinase inhibitor inhibits Cbl phosphorylation as well

as ubiquitination of the EGF receptor, Kassenbrock et al. do not teach that such inhibition would have an antagonistic effect on EphA2. In fact, the inhibition of Cbl phosphorylation would be expected to have the opposite effect and increase, rather than decrease EphA2 activity since Cbl phosphorylation is vital to its function. The latter is supported by the teachings of Wang et al. which establish that the "N-terminal tyrosine kinase-binding (TKB) domain plays a critical role in the association of Cbl with activated RTKs as well as in their negative regulation" (see bottom of first column on p. 217) in addition to the fact that "[a]n intact RING finger domain is essential for Cbl-mediated negative regulation of EphA2" (see first column on p.218) and that the phosphorylation of Cbl is essential for its association and inhibition of EphA2 (see Discussion on p.219). In fact, in support of Applicants argument, when the Cbl activity was diminished, a "dose-dependent increase in the levels of EphA2 was seen" (see second to the last paragraph of the Discussion). The phosphorylation-dependence of Cbl activation is also supported by the teachings of Kassenbrock et al. which teach that "phosphorylation of a tyrosine residue in the N-terminal half of c-Cbl may be required for ubiquitin ligase activity" whereas "PI3-kinase is regulated by a C-terminal phosphorylation event" (see last paragraph of Discussion). Accordingly, the art teaches against the Examiner's argument that inhibition of Cbl by PP1, a Src-kinase inhibitor, would be expected to lead to inhibition of EphA2. Accordingly, the cited publications provide neither the requisite motivation nor reasonable expectation of success required to properly support the Examiner's rejection of Claim 41.

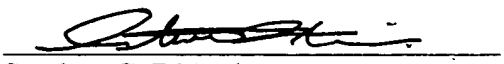
However, as noted *supra*, in the sole interest of facilitating prosecution, Applicants have amended Claim 41 to append the phrase "and wherein said protein tyrosine kinase inhibitor is an inhibitor of one or more of the following: Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, EphA1, and EphA2." Applicants believe the Examiner's rejection of Claim 41 under 35 U.S.C. § 103(a) has been overcome in consideration of this amendment and respectfully request that it be withdrawn. In addition, Applicants have rendered the Examiner's rejection of Claim 52 under 35 U.S.C. § 103(a) moot as a consequence of the cancellation of the same.

Applicants believe that all of the Examiners rejections and objections have been overcome and that all of the pending claims before the Examiner are in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

A three-month extension is hereby requested pursuant to 37 CFR §1.136(a). Please charge Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company in the amount of $1020 for payment of the extension fee.

If any fee is due in connection herewith not already accounted for, please charge such fee to Deposit Account No. 19-3880 of the undersigned. Furthermore, if any extension of time not already accounted for is required, such extension is hereby petitioned for, and it is requested that any fee due for said extension be charged to the above-stated Deposit Account.

Respectfully submitted,



Stephen C. D'Amico
Agent for Applicants
Reg. No. 46,652

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-5289

Date: September 14, 2006